

Leptomeningeal Metastasis of Malignant Lymphoma with Negative Results in Magnetic Resonance Imaging: A Case Report

Chih-Shan Huang¹, Hao-Wen Teng¹, Sey-En Lin², Chia-Yuen Chen³, Jia-Ying Sung¹

Abstract-

Non-Hodgkin's lymphoma which occasionally involves the central nervous system, occurs more often in high-grade cases and implicates a poor prognosis. Leptomeningeal metastases may present as multiple cranial nerve involvements. Diagnosis is achieved by recognizing the clinical manifestations, followed by neuroradiologic studies and laboratory examination of the cerebrospinal fluid. But normal studies of either method do not exclude such a diagnosis. We present one female patient with non-Hodgkin's lymphoma, who had multiple cranial nerve palsies as signs of central nervous system involvement, but who had negative results in her neuroimaging studies.

Key Words: cranial nerve palsy, non-Hodgkin's lymphoma, leptomeningeal metastasis, lymphomatosis

Acta Neurol Taiwan

INTRODUCTION

Leptomeningeal metastasis (LM), which is also called neoplastic meningitis (NM), is diagnosed in 1%-5% of patients with solid tumors (also being termed as carcinomatous meningitis), 5%-15% of patients with leukemia (leukemic meningitis) and lymphoma (lymphomatous meningitis), and 1%-2% of patients with primary brain tumors⁽¹⁾. Symptoms of LM include visual disturbances, headache, limb weakness, drowsiness or confusion, nausea and vomiting, numbness, or back pain. The oculomotor, abducens, and facial nerves are the most commonly affected cranial nerves⁽²⁾.

We report a patient who experienced subsequent

multiple cranial nerve palsies following malignant lymphoma originating in the neck, but the neuroimaging studies of the brain yielded negative results in the workup.

CASE REPORT

A 76-year-old woman patient had a history of diabetes mellitus, hypertension, colon cancer with status post hemicolectomy, and old infarction in the left cerebral hemisphere with right hemiparesis. She found to have a non-tender, firm, unmovable and rapidly growing mass in the right neck. The finding of the pathological examination of the biopsy specimen showed malignant

From the Departments of ¹Neurology, Radiology Taipei Medical University-Wan Fang Medical Center, ²Department of Pathology, Taipei Medical University, ³Department of Radiology, Taipei Medical University-Wan Fang Medical Center.

Received May 26, 2010. Revised June 24, 2010.

Accepted December 2, 2010.

Correspondence to: Jia-Ying Sung, MD. Department of Neurology Taipei Medical University-Wan Fang Medical Center, No. 111, Hsing-Long Road, Section 3, Taipei 116, Taiwan.

E-mail: 96317@wanfang.gov.tw

lymphoma, diffuse large B cell type, with bone marrow involvement. She was diagnosed as having high-grade (H)-non-Hodgkin's lymphoma (NHL), stage IV. She then received systemic chemotherapy and immunotherapy. After one course of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), five courses of CHP (cyclophosphamide, doxorubicin, and prednisolone) and three courses of rituximab, she achieved regression of the right neck lymphadenopathy with a study of the follow-up computed tomography (CT) scan.

At the 6th cycle of chemotherapy with CHP four

months after the diagnosis of lymphoma, the patient experienced double vision and retro-orbital pain in the right eye with eyelid drooping. Being conscious, she did not have headache and vomiting. The results of the neurological examination showed that she had a painful right oculomotor nerve palsy, and that she had reactive pupils. But the pupil on the right side was smaller. The fundoscopic examination revealed no evidence of papilloedema. Figure 1 is the Gadolinium-enhanced magnetic resonance imaging (Gd-MRI) of the brain. The result of her erythrocyte sedimentation rate was 25 mm/hr. The

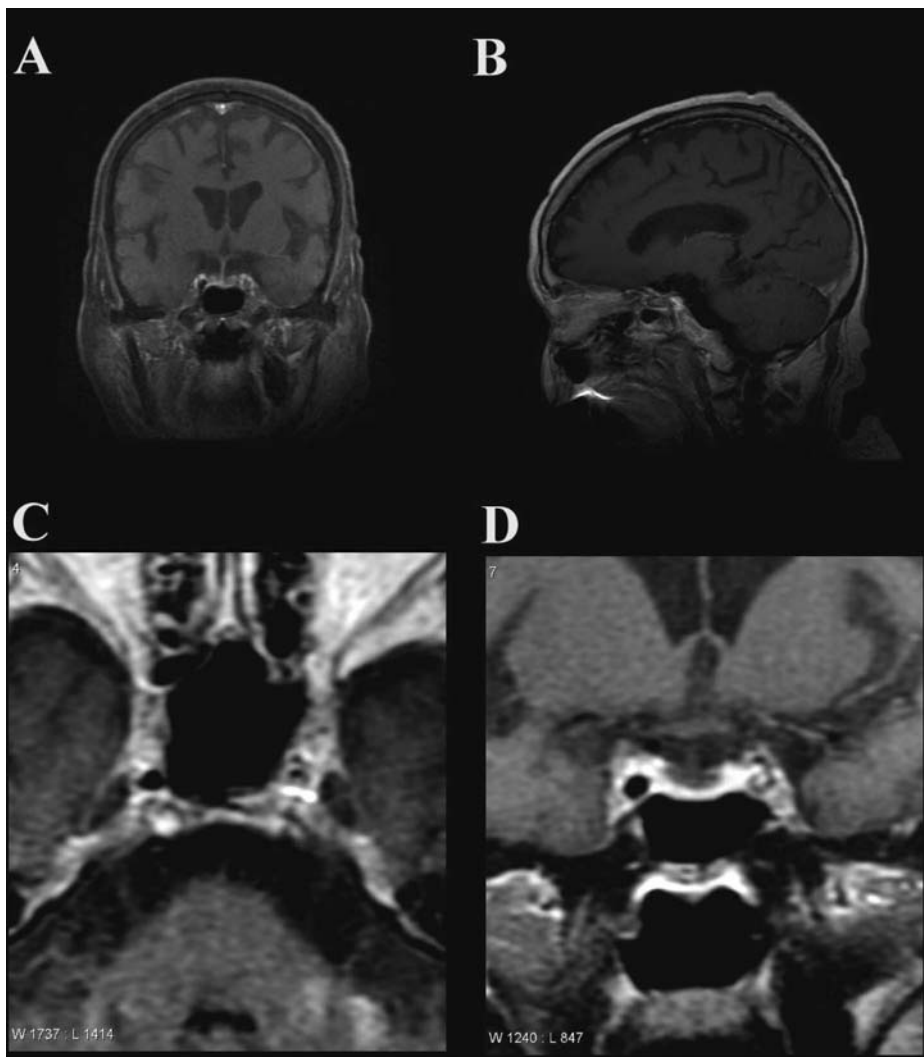


Figure 1. Gadolinium-enhanced magnetic resonance imaging (Gd-MRI) of the brain in T1-weighted image. There was no evidence of focal lesion in brain parenchyma, with coronary and sagittal view (Fig. 1-A and Fig. 1-B). It also showed no abnormal enhancement along the left oculomotor nerve (Fig. 1-C) or in the cavernous sinus (Fig. 1-D).

tentative diagnosis was diabetic cranial mononeuropathy or Tolosa-Hunt syndrome. Her HbA1C level was 6.1%. She kept receiving control of blood glucose with gli-clazide 15 mg/day and additional pentoxifylline 300 mg/day. The patient hesitated to receive a lumbar puncture and she returned home after the chemotherapy because she had improved spontaneously.

One month later, the patient visited our emergency department (ED) because of left mouth angle drooling with hyperacusis. She was suspected to have Bell's palsy and had received prednisolone 45 mg/day for one week. But she gradually became drowsy and mute. She had poor appetite and general weakness. She was brought to our oncology clinic one week later and was referred to the ED because of impaired consciousness. In neurological examination, she had a Glasgow Coma Scale (GCS) score of E3V1M5, she was found to have left abducens nerve palsy and left peripheral type facial nerve palsy, but she did not have any focal muscle weakness in limbs. The results of the laboratory data were normal. Her CT scan of the brain showed multiple small low-density lesions of old infarctions. She was admitted to

our neurology ward for further study.

The finding of the follow-up Gd-MRI of the brain showed focal encephalomalacia in the left periventricular region, remained unchanged as compared with that of last image study, and did not show any evidence of acute infarction or definite focal enhancement. The result of the cerebrospinal fluid (CSF) examination disclosed pleocytosis ($2,060 /\text{mm}^3$) and raised protein content (127.9 mg/dL), with a normal opening pressure ($150 \text{ mmH}_2\text{O}$) and glucose level (61 mg/dL , compared to 192 mg/dL in serum). Figure 2 showed the cytological picture of the CSF specimen. On the basis of those findings, we suspected that our patient had the LM of malignant lymphoma to cause oculomotor, abducens, and facial nerve palsies. We suggested giving her chemotherapy, but her family preferred to giving her palliative treatment instead. Therefore, the patient was referred to hospice care, and she died one week later.

DISCUSSION

The CNS involvement is rare in NHL, with a frequency of less than 10%⁽³⁻⁴⁾. Those patients are often resistant to both chemotherapy and radiation therapy, and have poor prognosis.

Diagnosis of CNS disease is frequently suspected in the presence of clinical manifestations of CNS involvement and positive findings of neuroimaging studies, and confirmed by conventional CSF cytological examinations⁽⁵⁾. Most of the reported cases show direct tumor invasion (classically known as Garcin syndrome, skull base tumor invasion) and accordingly, have allowed the diagnosis of LM⁽⁶⁾. To our knowledge, the enhancement of cranial nerves on MRI indicates neuropathies influenced by tumor infiltration. Our patient did not show abnormal enhanced lesion in brain parenchyma or definite focal lesion along oculomotor nerves. We initially considered that the patient had LM because the findings of CSF cytological studies suggested the infiltration of the lymphoma cells into the cranial nerves. But the negative results of neuroimaging study in our patient may indicate the existence of another mechanism associated with lymphoma inducing cranial neuropathy such as

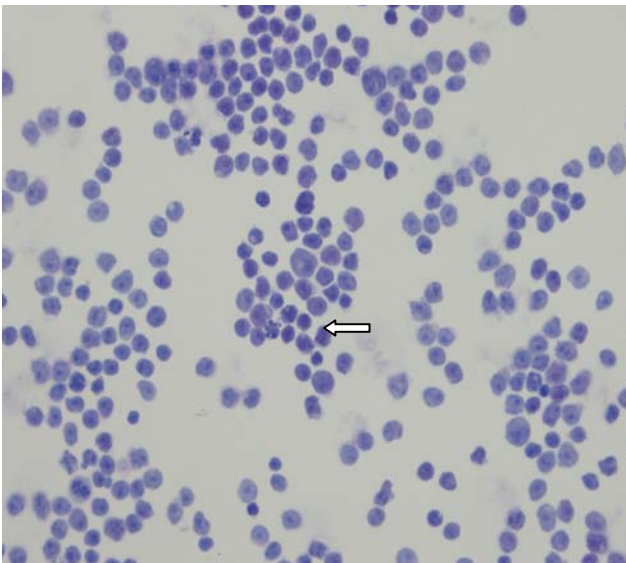


Figure 2. High cellularity with atypical lymphoid cells in the cerebrospinal fluid (CSF) smear (400X). The atypical cells had slightly irregular large nuclei, scanty cytoplasm, and prominent nucleoli (white arrow). The picture was consistent with a metastatic large cell lymphoma.

immunological disturbances causing the loss of myelin.

Initially, the patient had pupil-sparing oculomotor palsy. She received Gd-MRI of the brain for suspicious CNS metastasis because she had a history of malignant lymphoma. The neuroimaging results were negative. Thus, the oculomotor palsy was considered more likely to be associated with diabetic cranial mononeuropathy, which is the most common cranial nerve diabetic disorder.

In 1966, Rucker et al. reported 1,000 cases of palsies of the oculomotor, trochlear, and abducens nerves⁽⁷⁾. Among them, metastasis (98 cases, 9.8%) and vascular diseases (107 cases, 10.7%) accounted for the two most common causes of cranial neuropathy. But when multiple cranial nerve involvement has been taken into consideration, neoplasm is the much more common cause (47 cases) than vascular disease (1 case). Therefore, we suggest that those patients need to be carefully examined to exclude a possible malignancy.

Based on our experience in this case, we also suggest that all patients with malignant lymphoma or with multiple cranial nerve involvement should receive a lumbar puncture for cytological examinations of the CSF because the diagnosis of LM still cannot be excluded by negative neuroimaging results.

Frielich et al. found MRI evidence of leptomeningeal metastasis in 90% of patients with solid tumors, but 55% of patients with hematological malignancy⁽⁸⁾. Their hematological LM is less well demonstrated on MRI, than that from solid tumors⁽⁸⁾. Straathof et al. reported 61 patients with known cancer, compared the finding of Gd-MRI with that of the CSF cytology, and showed their equal sensitivity but different specificity⁽⁹⁾. Therefore, those two diagnostic tools for LM are both necessary in patients with malignancy⁽¹⁰⁾. Neither normal CSF nor MRI study finding excludes the diagnosis of LM, especially in hematological malignancy.

Hollender et al. conducted a study and established a risk model to guide clinicians to identify high-risk NHL patients and to decide whether they should receive intrathecal chemotherapy for CNS prophylaxis⁽¹¹⁾. In low-grade (L)-NHL, the risk of CNS involvement is found to be low. The patients with lymphoblastic,

Burkitt's and high-grade (H)-NHL have a higher risk of CNS recurrence⁽¹¹⁾. With multivariate analysis, they identified five independent risk factors: serum lactate dehydrogenase (LDH) > 450 U/l, serum albumin < 3.5 g/dl, < 60 years of age, retroperitoneal lymph node involvement, and the presence of more than one extranodal site⁽¹¹⁾. If 4 out of 5 of these risk factors are present, the risk of CNS recurrence is more than 25% in five years, suggesting that those high-risk patients should receive intensive prophylactic chemotherapy. Our patient had H-NHL with low serum albumin and involvement of the bone marrow. CNS prophylaxis may be considered, but is not mandatory. But the factors of being old in age and having poor performance status in our patient would also be reasons for not giving the more intensive therapy.

ACKNOWLEDGEMENT

Professor Winston W. Shen gave valuable editing comments in an earlier version of this manuscript.

REFERENCES

1. Chamberlain MC. Carcinomatous meningitis. *Arch Neurol* 1997; 54: 16-17.
2. Rowland LP. Lymphomas. In: Rowland LP Eds, Merritt's Textbook of Neurology, 11th edition. Philadelphia: Lippincott Williams & Wilkins, 2005; 406-407.
3. Herman TS, Hammond N, Jones SE, Butler JJ, Byrne GE Jr, McKelvey EM. Involvement of the central nervous system by non-Hodgkin lymphoma: the Southwest Oncology Group experience. *Cancer* 1979; 43: 390-397.
4. MacKintosh FR, Colby TV, Podolsky WJ, Burke JS, Hoppe RT, Rosenfelt FP, Rosenberg SA, Kaplan HS. Central nervous system involvement in non-Hodgkin's lymphoma: an analysis of 105 cases. *Cancer* 1982; 49: 586-595.
5. Bierman P, Giglio P. Diagnosis and treatment of central nervous system involvement in non-Hodgkin's lymphoma. *Hematol Oncol Clin North Am* 2005; 19: 597-609.
6. Toeh R, Barnard RO, Gautier-Smoth PC. Polyneuritis cranialis as a presentation of malignant lymphoma. *J Neurol Sci* 1980; 48: 399-412.
7. Rucker CW. The causes of paralysis of the third, fourth and

- sixth cranial nerves. *Am J Ophthalmol* 1966; 61: 1293-1298.
8. Freilich RJ, Krol G, De Angelis LM. Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastases. *Ann Neurol* 1995; 38: 51-57.
 9. Straathof CS, de Bruin HG, Dippel DW, Vecht CJ. The diagnostic accuracy of magnetic resonance imaging and cerebrospinal fluid cytology in leptomeningeal metastasis. *J Neurol* 1999; 246: 810-814.
 10. Enting RH. Leptomeningeal neoplasia : epidemiology, clinical presentation, CSF analysis and diagnostic imaging. *Cancer Treat Res* 2005; 125: 17-30.
 11. Hollender A, Kvaloy S, Nome O, Skovlund E, Lote K, Holte H. Central nervous system involvement following diagnosis of non-Hodgkin's lymphoma: a risk model. *Ann Oncol* 2002; 13: 1099-1107.